Hodgkin Lymphoma

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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Diagnosis/Initial Evaluation</td>
<td>Page 2</td>
</tr>
<tr>
<td>Classical Hodgkin Lymphoma Stage I-II</td>
<td>Pages 3-4</td>
</tr>
<tr>
<td>Classical Hodgkin Lymphoma Advanced Stages III, IV</td>
<td>Pages 5-6</td>
</tr>
<tr>
<td>Lymphocyte Predominant Hodgkin Lymphoma</td>
<td>Page 7</td>
</tr>
<tr>
<td>Follow-up After Completion of Treatment</td>
<td>Page 8</td>
</tr>
<tr>
<td>Salvage Therapy</td>
<td>Page 9</td>
</tr>
<tr>
<td>APPENDIX A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma</td>
<td>Page 10</td>
</tr>
<tr>
<td>APPENDIX B: Deauville Criteria</td>
<td>Page 10</td>
</tr>
<tr>
<td>APPENDIX C: Radiation Therapy Guidelines</td>
<td>Page 11</td>
</tr>
<tr>
<td>APPENDIX D: Response Criteria for Malignant Lymphoma</td>
<td>Page 12</td>
</tr>
<tr>
<td>APPENDIX E: International Prognostic Score (Hasenclever Index)</td>
<td>Page 13</td>
</tr>
<tr>
<td>APPENDIX F: Systemic Therapy for Relapsed or Refractory Disease</td>
<td>Page 14</td>
</tr>
<tr>
<td>Suggested Readings</td>
<td>Pages 15-17</td>
</tr>
<tr>
<td>Development Credits</td>
<td>Page 18</td>
</tr>
</tbody>
</table>
**Hodgkin Lymphoma**

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**NOTE:** Consider Clinical Trials as treatment options for eligible patients.

---

### ESSENTIAL:
- FNA alone is insufficient
- Hematopathology review of all slides with at least one tumor paraffin block. Rebiopsy if consult material is non-diagnostic. Core needle biopsy may be adequate if diagnostic, but an excisional nodal biopsy is recommended.
- Flow cytometry often not helpful
- Adequate immunophenotype to confirm diagnosis
  - Immunohistochemistry on paraffin panel for Hodgkin lymphoma (HL) including nodular lymphocyte predominant HL:
    - CD20, PAX-5, CD30, CD3, CD15, CD21, and CD45 (LCA)
    - EBER

### OF USE IN CERTAIN CIRCUMSTANCES:
- Immunohistochemical studies:
  - LMP1
  - BOB1, OCT2, and CD79a (differential diagnosis with B-cell lymphoma, unclassifiable with features intermediate between classical HL and DLBCL and primary mediastinal large B-cell lymphoma).
  - CD23, or CD35 (follicular dendritic cell markers), BCL6 in cases of nodular lymphocyte predominant HL (may help with T-cell/histiocyte rich large B-cell lymphoma)
  - CD2, CD43, ALK (differential diagnosis with anaplastic large cell lymphoma)

### STRONGLY RECOMMEND:
- Core biopsy for tissue banking by protocol

---

### INITIAL EVALUATION

**ESSENTIAL:**
- History and physical including:
  - Alcohol intolerance
  - Pruritus
  - Exam of nodes
  - B symptoms (Unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10% of body weight ≤ 6 months of diagnosis)
- CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, serum calcium, uric acid
- Erythrocyte sedimentation rate (ESR)
- Screening for HIV 1, HIV 2, hepatitis B and C (HBcAb, HBsAg, HCVAb)
- PET/CT with contrast
- Pulmonary Function Tests
- Consider bone marrow biopsy if there are cytopenias and/or inconclusive PET
- MUGA scan or echocardiogram
- Counseling: psychosocial if clinically indicated
- Lifestyle risk assessment
- Discuss fertility preservation

### OF USE IN SELECTED CASES:
- Chest x-ray, PA and LAT
- Pregnancy test
- Cardiology consultation at baseline if risk factors for cardiac toxicity [i.e., obesity, abnormal echocardiogram, hypertension (HTN), hyperlipidemia (HLD)]

---

1 See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice.
### Classical Hodgkin Lymphoma Stage I-II Combined Modality Therapy

#### CLINICAL PRESENTATION

- Classical Hodgkin Lymphoma Stage I-II with preference to treat with combined modality therapy

#### PRIMARY TREATMENT

- **ABVD** for 2 cycles
- **PET/CT**

#### RESPONSE EVALUATION

- **Deauville**
  - 1-3
  - 4
  - 5

#### TREATMENT

- **ABVD for 2 cycles followed by PET/CT**
- **Complete response**

- **Biopsy**
  - Yes → Multidisciplinary conference with disease site specialist
  - Multidisciplinary conference with disease site specialist
  - Excisional biopsy if available

- **No → Biopsy**
  - Yes → PET/CT
  - No → See Page 8: Follow-up After Completion of Treatment

---

1. See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
2. See Appendix B: Deauville Criteria
3. See Appendix C: Radiation Therapy Guidelines
4. See Appendix D: Response Criteria for Malignant Lymphoma

---

**NOTE:** Consider Clinical Trials as treatment options for eligible patients.

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---

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
ISRT = involved site radiation therapy
GHSG = German Hodgkin Study Group

---

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Hodgkin Lymphoma

Classical Hodgkin Lymphoma Stage I-II Chemotherapy Alone

NOTE: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>PRIMARY TREATMENT</th>
<th>RESPONSE EVALUATION</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| ABVD for 2 cycles | Deauville³ 1-2       | • ABVD for 1 to 2 cycles or AVD for 4 cycles
| PET/CT            |                      | • For initial stage IIB or ≥3 nodal regions or ESR > 50: AVD for 4 cycles (total 6 cycles) |
|                   | Deauville³ 3-4       | • ABVD for 2 cycles or AVD for 4 cycles
|                   |                      | • For initial stage IIB or ≥3 nodal regions with ESR > 50: AVD for 4 cycles (total of 6 cycles) |
|                   | Deauville³ 5         | Biopsy negative? |
|                   |                      | Yes → Multidisciplinary conference with disease site specialist |
|                   |                      | Biopsy negative? |
|                   |                      | No → See Page 9: Salvage Therapy |

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine

1 See Appendix A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma
2 A subset of patients who meet criteria as per the UK Rapid study with stage IA and stage IIA Hodgkin Lymphoma with no mediastinal bulk and negative PET findings after treatment may receive 3 cycles of chemotherapy with or without additional involved site radiation therapy (ISRT)
3 See Appendix B: Deauville Criteria

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See Page 8: Follow-up After Completion of Treatment

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Hodgkin Lymphoma

Classical Hodgkin Lymphoma Advanced Stages III, IV

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NOTE: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION

Primary Treatment

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
BV = brentuximab vedotin
IPS = International Prognostic Score
ISRT = involved site radiation therapy

1 Advanced stage is consistent with an IPS ≥ 4, age < 60 years [See Appendix E: International Prognostic Score (Hasenclever Index)]

2 Patients with IPS ≥ 4 and age < 65 years may benefit from ABVD. Patients with underlying neuropathy should proceed with caution.

3 Patients who are at higher risk for bleomycin lung toxicity should be considered for BV-AVD.

4 See Appendix C: Radiation Therapy Guideline

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CLINICAL PRESENTATION

Hodgkin Lymphoma

Classical Hodgkin Lymphoma Advanced Stages III, IV

NOTE: Consider Clinical Trials as treatment options for eligible patients.

RESPONSE EVALUATION

TREATMENT

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
ISRT = involved site radiation therapy

1 Advanced stage is consistent with an International Prognostic Score ≥ 4, age < 60 [See Appendix E: International Prognostic Score (Hasenclever Index)]

2 See Appendix B: Deauville Criteria

3 See Appendix C: Radiation Therapy Guideline
Hodgkin Lymphoma

Lymphocyte Predominant Hodgkin Lymphoma

CLINICAL PRESENTATION

- Lymphocyte Predominant Hodgkin Lymphoma Stages IA, IIA (non-bulky)
  - Observe or ISRT

- Lymphocyte Predominant Hodgkin Lymphoma Stage IIA (bulky)
  - Rituximab or ISRT
  - Consider R-CHOP for bulky, subdiaphragmatic, or splenic disease followed by involved site radiation therapy for patients with bulky disease

- Lymphocyte Predominant Hodgkin Lymphoma Stages IB, IIB
  - Rituximab or ISRT
  - Consider R-CHOP for bulky, subdiaphragmatic, or splenic disease followed by involved site radiation therapy for patients with bulky disease

- Lymphocyte Predominant Hodgkin Lymphoma Stages III, IV
  - Rituximab or R-CHOP for 3-6 cycles
  - Consider ISRT to bulky sites following R-CHOP

PRIMARY TREATMENT

INITIAL RESPONSE EVALUATION

- Observe if asymptomatic
- PET/CT negative?
  - Yes: Observe
  - No: Biopsy
  - Biopsy negative?
    - No: Salvage Therapy
    - Yes: Multidisciplinary conference with disease site specialist, Excisional biopsy if available

ISRT = involved site radiation therapy
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

1 See Appendix C: Radiation Therapy Guideline

NOTE: Consider Clinical Trials as treatment options for eligible patients.

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**Hodgkin Lymphoma**

**FOLLOW-UP AFTER COMPLETION OF TREATMENT**

- Follow-up with an oncologist is recommended
- Interim history and physical: every 4 months for years 1 and 2, then every 6 months for year 3, then annually
- Pneumococcal and meningococcal revaccination if patient treated with splenic radiation therapy: See Management of Adult Asplenic/Hyposplenic Patients algorithm
- Annual influenza vaccine (especially if patient treated with bleomycin or chest radiation therapy)
- Laboratory studies:
  - CBC with differential, LDH, BUN, creatinine, albumin, AST, ALT, total bilirubin, alkaline phosphatase, serum calcium, uric acid every 4 months for years 1 and 2, then every 6 months for years 3, then annually
  - TSH every 6 months if radiation therapy to neck and optional for all other cases
- CT neck, chest, abdomen and pelvis with contrast at 6, 12, and 24 months or as clinically indicated. PET/CT only if last PET was Deauville 4-5, to confirm complete response
- Annual breast screening: initiate alternating mammography and MRI 8 years post therapy or at age 40, whichever is sooner, if radiation therapy above diaphragm
- Counseling: reproduction, health habits, psychosocial, cardiovascular, breast self-exam, skin cancer risk, end-of-treatment discussion
- Recommend written follow-up instructions for the patient
- Stress test/echocardiogram at 10-year intervals after treatment is completed
- Consider carotid ultrasound at 10-year intervals if neck irradiation

---

**NOTE:** Consider Clinical Trials as treatment options for eligible patients.
SALVAGE THERAPY

**AHSCT** = autologous hematopoietic stem cell transplant

**BV** = brentuximab vedotin

**CAR** = chimeric antigen receptor

1. See Appendix D: Response Criteria for Malignant Lymphoma
2. Conventional-dose chemotherapy may precede high-dose therapy. Sequence of therapy may vary.
3. Perform biopsy if plan to treat with high-dose chemotherapy
4. Extranodal disease (i.e., any tumor spread that involves tissues other than those of the lymph nodes, spleen, thymus, Waldeyer’s tonsillar ring, appendix, and Peyer’s patches)
5. Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis
6. See Appendix F: Systemic Therapy for Relapse or Refractory Disease

**NOTE:** Consider Clinical Trials as treatment options for eligible patients.

**RESPONSE EVALUATION**

Relapse or Refractory disease → Systemic therapy for relapse or refractory disease (see Appendix F) followed by PET/CT

- Complete response¹
- Partial response¹

Consider changing to different regimen⁶ →

- Complete response or near complete response?

No →

- Progressive disease post AHSCT?
  - Yes →
    - Consider allogetic stem cell transplant or Clinical or CAR T-cell therapy trial
  - No →
    - See Page 8: Follow-up After Completion of Treatment

Yes →

- AHSCT²,³ with or without locoregional radiation therapy
- Consider maintenance BV for patients with primary refractory disease or any of the following risk factors:
  - Early relapse < 12 months
  - Extranodal disease⁴ at time of relapse
  - Not in CR at time of AHSCT
  - B symptoms⁵
  - Greater than 1 salvage/subsequent therapy regimen

- Consider gemcitabine-based chemotherapy or immunotherapy or other cellular therapies if not previously given or Clinical trial

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Hodgkin Lymphoma

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APPENDIX A: Unfavorable Risk Factors for Stage I-II Classic Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms¹</td>
<td>ESR &gt; 50 mm/hour if A; ESR &gt; 30 mm/hour if B</td>
<td>ESR &gt; 50 mm/hour if A; ESR &gt; 30 mm/hour if B</td>
<td>ESR ≥ 50 mm/hour or any B symptoms¹</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; 0.33</td>
<td>MTR &gt; 0.35</td>
<td>MMR &gt; 0.33</td>
</tr>
<tr>
<td># Nodal sites</td>
<td>Area ≥ 3²</td>
<td>Sites &gt; 3²</td>
<td>Sites &gt; 3</td>
</tr>
<tr>
<td>E lesion</td>
<td>any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky³</td>
<td></td>
<td>Size &gt; 10 cm</td>
<td></td>
</tr>
</tbody>
</table>

A = no B symptoms
GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6
NCCN = National Comprehensive Cancer Network

¹ Unexplained fever > 38°C during the previous month, recurrent drenching night sweats during the previous month, weight loss > 10% of body weight ≤ 6 months of diagnosis
² The EORTC includes the infraclavicular/subpectoral area with the axilla area while the GHSG includes this area with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.
³ Bulky may be defined as MMR > 0.33 or any mass > 10 cm in size

APPENDIX B: Deauville Criteria

- Score 1: no uptake
- Score 2: uptake less than or equal to mediastinum
- Score 3: uptake greater than mediastinum but less than or equal to liver
- Score 4: uptake greater than liver at any site
- Score 5: uptake greater than liver and new sites of disease
- Score X: new areas of uptake unlikely to be related to lymphoma

A score of 1-3 is regarded as negative and 4 or 5 as positive

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Consider intensity-modulated radiation therapy (IMRT) or proton therapy, as appropriate, to minimize toxicity.

Dose if radiation therapy is given alone:
30-45 Gy, depending on treatment intent, disease bulk, etc.

Doses for combined modality radiation therapy:
- Early stage favorable: 20 Gy to involved site
- Early stage unfavorable: 30 Gy to involved site

Salvage radiation therapy when Deauville $\geq 4$:
36-45 Gy, depending on disease bulk and response to chemotherapy

Radiation Fields:
Involved Site Radiation Therapy: Treatment of involved lymph nodes regions only

1 See Appendix B: Deauville Criteria
# APPENDIX D: Response Criteria for Malignant Lymphoma

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
</table>
| **CR** (Complete Response: disappearance of all evidence of disease) | - FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative  
- Variably FDG-avid or PET negative; regression to normal size on CT | Not palpable, nodules disappeared                                                                | Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative |
| **PR** (Partial Response) | - Decrease of ≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes  
- FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site  
- Variably FDG-avid or PET negative; regression on CT | Decrease of ≥ 50% in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen | Irrelevant if positive prior to therapy; cell type should be specified |
| **SD** (Stable disease: failure to attain CR/PR or PD) | - FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET  
- Variably FDG-avid or PET negative; no change in size of previous lesions on CT | -                                                                                 |                                                                                 |
| Relapse or Progressive disease  
(Any new lesion or increase by ≥ 50% of previously involved sites from nadir) | - Appearance of a new lesion(s) > 1.5 cm in any axis,  
≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis  
- Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy | Increase of ≥ 50% from nadir in the SPD of any previous lesions | New or recurrent involvement |

FDG, $[^{18}F] = \text{fluorodeoxyglucose}$  
SPD = sum of the product of the diameters  
Hodgkin Lymphoma

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APPENDIX E: International Prognostic Score (Hasenclever Index¹)

- Albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age ≥ 45 years
- Stage IV disease
- White blood cell count ≥ 15 K/microliter
- Lymphocyte count < 8% of white blood cell count, and/or lymphocyte count < 0.6 K/microliter

Each factor = 1 point

Hodgkin Lymphoma

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APPENDIX F: Systemic Therapy for Relapsed or Refractory Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chemotherapy Options</th>
<th>Subsequent Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic Hodgkin Lymphoma</td>
<td>- Brentuximab vedotin&lt;br&gt;- Brentuximab vedotin plus bendamustine&lt;br&gt;- Brentuximab vedotin plus nivolumab &lt;br&gt;- DHAP (dexamethasone, cisplatin, high dose cytarabine) &lt;br&gt;- ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin) &lt;br&gt;- Gemcitabine/bendamustine/vinorelbine &lt;br&gt;- BGVD (gemcitabine, vinorelbine, liposomal doxorubicin) &lt;br&gt;- ICE (ifosfamide, carboplatin, etoposide) &lt;br&gt;- IGEV (ifosfamide, gemcitabine, vinorelbine)</td>
<td>- Bendamustine&lt;br&gt;- Everolimus&lt;br&gt;- GCD (gemcitabine, carboplatin, dexamethasone)&lt;br&gt;- Lenalidomide&lt;br&gt;- MINE (etoposide, ifosfamide, mesna, mitoxantrone)&lt;br&gt;- Mini-BEAM (carmustine, cytarabine, etoposide, melphalan)&lt;br&gt;- Nivolumab&lt;br&gt;- Prembrolizumab</td>
</tr>
<tr>
<td>Lymphocyte Predominant Hodgkin Lymphoma</td>
<td>- Rituximab plus DHAP (dexamethasone, cisplatin, high dose cytarabine)&lt;br&gt;- Rituximab plus ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin)&lt;br&gt;- Rituximab plus ICE (ifosfamide, carboplatin, etoposide)&lt;br&gt;- Rituximab plus IGEV (ifosfamide, gemcitabine, vinorelbine)</td>
<td></td>
</tr>
</tbody>
</table>

1 Subsequent options also include chemotherapy options that were not previously given
Hodgkin Lymphoma

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SUGGESTED READINGS


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Continued on next page


Hodgkin Lymphoma

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Lymphoma Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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- Loretta Nastoupil, MD (Lymphoma/Myeloma)
- Chelsea Pinnix, MD, PhD (Radiation Oncology)
- Felipe Samaniego, MD (Lymphoma/Myeloma)
- Raphael E. Steiner, MD (Lymphoma/Myeloma)
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\(^T\)Core Development Team Lead
\(^a\)Clinical Effectiveness Development Team